Unsupervised gland segmentation on stained histological whole slide images

By Qixiang Zhang

Background and Key Problem. Gland segmentation from whole slide images (WSIs) is a crucial step to obtain statistics that reveal the aggressiveness of tumors. Recently, by virtue of the development of deep learning techniques, training neural networks to perform automatic gland segmentation has aroused significant attention [1]. However, the performance of most existing methods highly relies on the large number of annotations which consumes a huge amount of manpower. To reduce the annotation cost, it is desirable to design a label-efficient method for gland segmentation. Currently, label-efficient methods such as weakly supervised semantic segmentation (WSSS) [2] and unsupervised semantic segmentation (USSS) [3], have been widely utilized in natural image analysis. However, there are few studies for label-efficient WSI segmentation, especially for glandular datasets, with the only exception of one study [4] on weakly supervised gland segmentation, let alone related research on the unsupervised setting.

Although there are multiple general label-efficient segmentation methods in computer vision, these methods usually cannot work well on glandular datasets. Li et al. [4] proved that existing general WSSS methods do not suit glandular datasets on account of *confusion among classes*. Furthermore, in my preliminary experiments, general USSS methods [3, 7, 8] trying to train the model with pseudo cluster labels in a self-supervised manner, also perform badly on GlaS [5] dataset. The major reason for this phenomenon is that, representations in one same object (i.e., gland) vary from each other, which makes it extremely difficult to group pixels from the same class together. For glandular datasets, the root cause lies in the *intra-class variance*, as each gland usually contains certain different regions with variant color distributions and morphological features. And how to design an unsupervised segmentation method that can adapt to *intra-class variance* becomes the essential task to improve the performance of unsupervised gland segmentation, which is also the primary goal of my research proposal. Actually, I have already made some progress which will be discussed in the next section.

Research Method. Previous unsupervised segmentation techniques applied on the general object datasets usually try to directly segment the entire foreground, which is really difficult for glandular datasets on account of *intra-class variance*. To solve this problem, instead of segmenting entire gland once for all, I propose to first split the hard region (i.e., gland) into two easy regions (i.e., exterior region and interior region) with high-level intra-region similarity for unsupervised segmentation, and then aggregate these two easy regions back into the whole glandular tissue. The proposed training procedure is split into two stages. **In the first stage**, I plan to segment out the exterior region of glandular tissues which can be treated as “edges” of glands. To achieve this, a shallow convoluted neural network is implemented and trained with a typical self-supervised loss [8] and a designed *spatial loss*. The objective of the *spatial loss* is to minimize

variance across pixels adjacent to each other. With *spatial loss,* the model could better understand the spatial relationships across pixels, and consequently better group the spatially connected regions (e.g., edges of tissues). Then after successfully segmenting the exterior region, we could obtain interior regions of a few glandular tissues, by exploiting postprocess techniques to fill the surrounded areas of those well-segmented exterior regions. Please note that only a few glandular tissues' exterior regions can be well-segmented due to the limited performance of unsupervised model. We regard these filled interior region as a *prior knowledge* to guide the segmentation of interior region.
In the second stage, all of the training samples and the processed pseudo masks generated in the first stage will be used to train a PSPNet [6] in a fully supervised manner. Meanwhile, an original *knowledge diffusion loss* is applied to diffuse the introduced *prior knowledge*. Our key objective is to increase the similarity between the pseudo-region embedding of exterior regions and the previously introduced interior regions. In this way, we could force the model to understand that the exterior and interior region belong to one same semantic (i.e., gland), and propagate the *prior knowledge* to all glandular tissues. Specifically, I first aggregate features of exterior regions to summarize its region-level semantic information to a compact embedding vector. Then, I try to measure the variance between each pixel of previously introduced interior region and the above region-level embedding vector with mean squad error loss.

Preliminary Results and Future Plan. About the aforementioned unsupervised gland segmentation method, I have already conducted several experiments and gained promising results. I choose and reproduce some existing SOTA USSS methods (e.g., PiCIE [3], DeepCluster [7], IIC [8]) on GlaS [5] dataset. Among these methods, PiCIE performs best with only 39.3% at mIOU, while a randomly initialized network can already reach 34.3%. However, after the first stage, my proposed method can already achieve 41.1% at mIOU. With the involved *prior knowledge*, it is able to reach 49.3% on the training set. Furthermore, with pseudo labels of the training set, my proposed *knowledge diffusion loss* can finally help PSPNet to achieve 56.3%, significantly outperforming PiCIE with **17.0%** at mIOU. In the future, I will conduct comparison experiments and ablation studies on another glandular dataset, i.e., the CRAG [9] dataset to verify the robustness of proposed method and effectiveness of each proposed module.

Research Significance. As mentioned in the Background Section, building a label-efficient method for gland segmentation is crucial, while only few studies focus on this field. To my best knowledge, there is no specially designed unsupervised gland segmentation method, while existing general unsupervised segmentation techniques fail on the glandular datasets. Consequently, my proposed work will be the **first** unsupervised gland segmentation method, providing a **brand new** and more importantly feasible idea. Hopefully, this work can attract more attention to unsupervised gland segmentation.

Related Research Experiences. In June 2021, I started to work as a research member at the Medical Imaging Research Group of Sichuan University, supervised by Prof. Yan Wang. During this period, I have been involved in 2 related projects. **In December 2021**, I finished my journal paper: *Judge Like a Real Doctor: Dual Teacher Sample Consistency Framework for Semi-Supervised Medical Image Classification*. **In March**

2022, another paper that I participated in: *Multi-level Progressive Transfer Learning for Cervical Cancer Dose Prediction* has been finished and submitted to journal Medical Image Analysis. These two projects related to label-efficient methods not only enabled me to gain experience in independent study and paper writing, but also helped me obtain a deeper understanding in label-efficient medical image analysis. Armed with these research experience, I believe I can cope with various challenging tasks in my upcoming studies.

Reference

[1] K. M, et al. "A generalized deep learning framework for whole-slide image segmentation and analysis." Scientific reports. 2021.

[2] W. Y, et al. "Self-supervised equivariant attention mechanism for weakly supervised semantic segmentation." Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition. 2020.

[3] C. J. H, et al. "Picie: Unsupervised semantic segmentation using invariance and equivariance in clustering." Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition. 2021.

[4] L. Y, et al. "Online Easy Example Mining for Weakly-supervised Gland Segmentation from Histology Images." arXiv. 2022.

[5] S. K, et al. "Gland segmentation in colon histology images: The glas challenge contest." Medical image analysis. 2017.

[6] Z. H, et al. "Pyramid scene parsing network." Proceedings of the IEEE conference on computer vision and pattern recognition. 2017.

[7] T. K, et al. "Deepcluster: A general clustering framework based on deep learning." Joint European conference on machine learning and knowledge discovery in databases. 2017.

[8] J. X, et al. "Invariant information distillation for unsupervised image segmentation and clustering." arXiv. 2018.

[9] G. S, et al. "MILD-Net: Minimal information loss dilated network for gland instance segmentation in colon histology images." Medical image analysis. 2019.